Br. J. clin. Pharmac. (1982), **14**, 207–211

THE EFFECT OF INTRAVENOUS CIMETIDINE ON THE ABSORPTION OF ORALLY ADMINISTERED DIAZEPAM AND LORAZEPAM

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1 The effect of intravenous cimetidine 200 mg or 400 mg on the absorption of lorazepam 2.5 mg tablet and diazepam 10 mg tablet and capsule was studied.

2 Considerable individual variation in plasma concentrations was found with all preparations.

3 Cimetidine increased the absorption of diazepam and lorazepam.

4 Capsule preparations of diazepam generally produced higher drug plasma concentrations than the tablets.

Introduction

Cimetidine interferes with the clearance of a number of drugs, including diazepam in man (Klotz & Reimann, 1980). This could be of clinical importance in anaesthetic practice with the increasing popularity of oral diazepam as premedication (Haslett & Dundee, 1968; Steen & Hahl, 1969; McCaughey & Dundee, 1972). Many patients may be taking cimetidine, or given it preoperatively as a prophylaxis against acid aspiration (Johnston *et al.*, 1982a,b). Gastric acidity can be reduced by an emulsion antacid, and it is known that the concomitant administration of aluminium hydroxide gel increases both the peak plasma concentration and soporific effect of oral diazepam (Gamble, 1975).

This paper reports a study which evaluates whether the doses of cimetidine given in anaesthetic practice (200 and 400 mg i.v.) affect plasma levels of diazepam. Lorazepam was also included in the study as this is a popular oral preanaesthetic medication (Comer *et al.*, 1973; Gale & Galloon, 1976) which has proved highly acceptable to nurses and patients. Furthermore lorazepam is eliminated by direct glucuronidation which is not affected by cimetidine (Klotz & Reimann, 1980, 1981).

Carried out in a purely clinical situation with blood sampling done before induction of anaesthesia, this study deals simply with plasma levels during the first 3 h after administration. It is not a pharmacokinetic study dealing with elimination of either of these drugs.

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Methods

The subjects were adult female patients fasting from early morning who were scheduled for afternoon minor gynaecological operations. They were resting in bed and prepared for surgery. An upper age limit of 60 years and an upper weight limit of 90 kg were set and only patients conforming to grades 1 or 2 of the American Society of Anesthesiologists classification of physical status were included. Patients taking tranquillisers or hypnotics or any other current drug therapy were excluded as were heavy smokers and those patients who, despite assertions to the contrary, were found to have such a drug in the control plasma sample.

The nature of the investigation was explained to each subject and verbal consent obtained for venous cannulation and blood sampling. It was pointed out that the sedative/hypnotics to be given are in common use as premedicants.

The patients were randomly divided into two groups. Each received either saline 2 ml or cimetidine 200 mg or 400 mg by i.v. injection into a large forearm vein 30 min before receiving by mouth a tablet or capsule. The first group recceived lorazepam 2.5 mg tablet (Ativan, Wyeth), group 2 patients received diazepam 10 mg tablet or capsule (Valium, Roche). This gave a grand total of 9 patient groups which were broadly comparable with respect to average age and weight (Table 1). An individually 'heparinised' cannula was inserted for repeated blood sampling.

Each patient had a 5 ml 'control' sample taken before any drug was given and 30 min following injection of the saline or cimetidine. The patient then

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Table 1 Patient data (mean ± s.e. mean)

Drug preparation and adjunct	*Number*	*Average age (years)*	*Average weight (kg)*
Lorazepam + saline 2 ml	7	29 ± 2.3	59 ± 3.7
Lorazepam + cimetidine 200 mg	7	36 ± 4.2	50 ± 2.3
Lorazepam + cimetidine 400 mg	6	36 ± 4.5	57 ± 2.7
Diazepam tablet + saline 2 ml	5	29 ± 2.7	60 ± 3.1
Diazepam tablet + cimetidine 200 mg	5	39 ± 5.4	61 ± 2.9
Diazepam tablet + cimetidine 400 mg	5	30 ± 2.2	56 ± 2.2
Diazepam capsule + saline 2 ml	5	41 + 6.0	58 ± 4.1
Diazepam capsule + cimetidine 200 mg	5	30 ± 4.7	62 ± 5.6
Diazepam capsule + cimetidine 400 mg	5	32 ± 5.4	29 ± 4.2

received the oral premedicant and subsequent samples were withdrawn at 15, 30, 45, 60, 90, 120 and 180 min following administration. The study period was limited to 3 h, as this is the maximum time before operations when one would normally give premedication. Blood was immediately transferred to labelled heparinised tubes which were stored at 4°C and centrifuged within a maximum of 4 h. They were subsequently centrifuged (3,000 rev/min for 10 min) and the plasma placed in plain polystyrene tubes to be stored at −20°C until analysis.

Plasma lorazepam and diazepam estimations were by gas-liquid chromatography (Howard *et al.*, 1977; Gamble *et al.*, 1975). Cimetidine does not interfere with either of these determinations.

Results

There was considerable individual variation in the plasma concentrations of both benzodiazepines.

Mean plasma lorazepam concentrations following lorazepam 2.5 mg alone or following cimetidine are given in Figure 1. Both doses of cimetidine produced higher plasma lorazepam concentrations at all time intervals, the highest concentrations being found following 400 mg. However, the increase was only statistically significant following the higher dose of cimetidine at 15 ($P < 0.01$), 45 and 90 ($P < 0.05$) min. The mean peak plasma concentrations following lorazepam 2.5 mg given alone was 31.3 ± 4.86 ng ml^{-1} which was lower than that found following cimetidine 200 mg (35.0 ± 1.90 ng ml^{-1} and cimetidine 400 mg (38.7 ± 4.49 ng ml^{-1}). The differences are not statistically significant.

Average diazepam concentrations following 10 mg tablets or capsules given alone or following two doses of cimetidine are given in Table 2. Absorption from the capsule was found to be as variable as that from the tablet but it did produce slightly higher average plasma concentrations throughout the period of study. Cimetidine administration resulted in higher

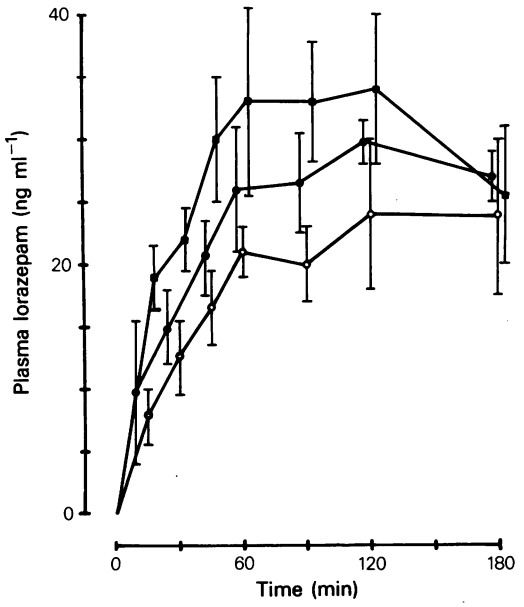

Figure 1 Mean ± s.e. mean plasma levels following 2.5 mg lorazepam by mouth given alone (○) or preceded by 200 mg cimetidine (●) or 400 mg given i.v. (■) 30 min prior to the benzodiazepine.

plasma concentrations of diazepam, particularly following the higher dose, the effect being more marked with the tablets over the first 45 min of the study. Differences however were not statistically significant.

Table 3 gives the mean peak diazepam concentrations and shows that cimetidine caused a dose-related increase with both tablets and capsules. The latter produced consistently higher levels but the only statistically significant result was when cimetidine 400 mg preceded the tablets. Cimetidine 400 mg also significantly shortened the mean time interval to the

Table 2 Mean ± s.e mean diazepam levels (ng ml^{-1}) over 180 min following 10 mg tablet (T) or capsule (C) orally, given alone or preceded by cimetidine 200 mg or 400 mg i.v.

		Time (min)						
	n	*15*	*30*	*45*	*60*	*90*	*120*	*180*
T	5	61.4 ± 20.33	120.0 ± 24.72	131.4 ± 19.28	137.8 ± 13.87	124.0 ± 15.65	97.0 ± 7.63	71.4 ± 10.63
T + cimetidine 200	5	79.2 ± 39.46	145.0 ± 27.58	140.6 ± 18.98	159.0 ± 7.56	146.8 ± 14.92	117.4 ± 21.54	85.6 ± 14.27
T + cimetidine 400	5	119.6 + 40.87	184.8 ± 18.44	176.4 ± 10.50	133.8 ± 6.97	107.0 ± 10.14	84.0 ± 13.52	79.2 ± 9.06
C	5	68.0 ± 32.04	147.4 ± 27.96	170.6 ± 26.45	173.0 ± 24.68	158.0 ± 13.90	138.2 ± 19.62	101.2 ± 7.53
C + cimetidine 200	5	59.6 ± 26.73	160.2 ± 21.39	197.8 ± 20.80	176.6 ± 22.54	135.0 ± 12.89	116.6 ± 12.20	91.4 ± 3.93
C + cimetidine 400	5	66.6 ± 22.55	185.8 ± 33.32	187.8 ± 15.43	177.4 ± 13.26	139.2 ± 10.53	123.6 ± 8.62	111.6 ± 13.05

Table 3 Mean peak (± s.e. mean plasma levels (ng ml^{-1}) of diazepam when these are given 30 min after an intravenous injection of saline or 200 mg or 400 mg cimetidine. There were 5 patients in each series.

Pre-treatment	*Diazepam*	
	Tablet	*Capsule*
Saline	151 ± 15	195 ± 21
Cimetidine 200 mg	191 ± 11	199 ± 20
Cimetidine 400 mg	202 ± 5*	207 ± 26

*$P < 0.02$ compared with saline pre-treatment group.

peak plasma concentration following the tablet (54.0 ± 10.17 min; compared with 30.0 ± 4.74 min; $P < 0.05$), although not with the capsule (60.0 ± 13.41 min; compared with 45.0 ± 6.71 min; $P < 0.40$).

Discussion

The effects of anaesthesia and operation limited this study to 180 min and it was not possible to estimate clearance of either benzodiazepine. The latter may be important as delayed clearance could result in higher plasma levels. Clearance of unbound diazepam tends to be higher in women than in men (Greenblatt *et al.*, 1980), but this variable was eliminated in the present study. It is also known that smoking increases diazepam clearance, particularly in young subjects, and while this may have contributed to the individual variations in readings it is not likely to have been very important as our choice of patients excluded heavy smokers.

The stomach is normally a relatively unimportant absorption site due to its small absorptive surface area and the effect of rapid gastric emptying (Levine, 1970; Nimmo, 1976; Prescott, 1974). However, gastric absorption of a drug could be significant if the environment pH is favourable and the drug remains in the stomach long enough to be absorbed. In one of the earliest studies into the effects of antacids on gastric absorption, Travell (1940) demonstrated that bases and alkaloids, such as strychnine, were well absorbed from the ligated stomach of experimental animals when the milieu was rendered alkaline with sodium bicarbonate. Further evidence that the pH of the environment dictates to a certain extent drug absorption is given in the pH partition hypothesis (Brodie & Hogben, 1957; Schanker, 1961).

Various studies investigating the influence of antacids on drug absorption have been complicated by differences in the antacids themselves. Magnesium hydroxide and calcium carbonate increase gastric pH much more than aluminium hydroxide (Hurwitz, 1977). Aluminium hydroxide delays gastric emptying in both rats and man (Hurwitz *et al.*, 1976) and

magnesium trisilicate binds other drugs to a greater extent than other antacid compounds (Hurwitz, 1977).

There are no primary effects of cimetidine on upper gastrointestinal motor function (Heading *et al.*, 1977) and it can be assumed that the changes reported here could be due to alterations in gastric acidity. Our findings could be explained on the basis of the dissociation constants (pKa) which are 3.4 for diazepam and 1.3 for lorazepam. Increases in gastric pH would enhance the absorption of the weakly basic benzodiazepines from the stomach, and it is possible that the higher benzodiazepine plasma levels following cimetidine may be due to increased gastric absorption. The increased uptake of diazepam is similar to that reported by Gamble (1975) when the drug was administered with aluminium hydroxide mixture (Aludrox).

The effect of cimetidine, although somewhat variable, was reasonably predictable in these studies. The situation is more complex when one considers its administration to patients who are being treated with enteric coated preparations. Morrison *et al.* (1980) found that although the coating should be soluble at pH 5 to 7, the bioavailabilty of prednisolone from an enteric-coated formulation was not affected by cimetidine under circumstances similar to those in which both drugs would be used by patients. Fisher *et al.* (1980) found reduced absorption of tetracycline with singles dose administration, but Garty & Hurwitz (1980) did not find this with chronic administration. To complicate matters, Breckenridge *et al.* (1979) found that cimetidine increased the action of warfarin in man by inhibition of drug metabolism.

For obvious reasons it was not possible to do concomitant studies of sedation in these patients, nor have we any clinical impression as to increased drowsiness in patients given cimetidine. However, on the basis of previous work (Gamble, 1975) one would expect the differences in mean diazepam levels in Tables 2 and 3 to be of clinical importance.

Our thanks are due to Dr D. Hurwitz and other anaesthetic staff of the Samaritan Hospital, Belfast for their cooperation and to Messrs P.J. Howard and W. Toner for analyses of samples.

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(Received December 7, 1981, accepted March 23, 1982)